DOCKET NO.: 0010-1106-0

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF		:
HITOO NISHINO ET AL.		: EXAMINER: KISHORE, G.
SERIAL NO: 09/556,701		:
FILED: APRIL 24, 2000		: GROUP ART UNIT: 1615
FOR:	PHARMACEUTICAL OR FOOD COMPOSITION FOR TREATMENT OR PREVENTION OF BRAIN EDEMA	:

APPEAL BRIEF

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

This is an appeal from the Final Rejection of the claims dated December 2, 2002.

I. REAL PARTY IN INTEREST

The real party in interest is Ajinomoto Co., Inc. by virtue of the assignment recorded August 30, 2000 at Reel/Frame 011054/0264.

II. RELATED APPEALS AND INTERFERENCES

Appellants, Appellants' legal representative and their assignee are not aware of any appeals or interferences which will directly affect or be directly affected by or having a bearing on the Board's decision in this appeal.

III. STATUS OF THE CLAIMS

The appealed claims are Claims 1-3, 7, 8, 12, 16, and 17, which are the only claims in the case.

IV. STATUS OF THE AMENDMENTS FILED UNDER 37 C.F.R. §1.116

No amendments to the claims have been filed subsequent to the mailing of the Final Rejection on December 2, 2002.

V. THE APPEALED CLAIMS

A copy of the appealed claims is submitted in the Appendix attached hereto.

VI. SUMMARY OF THE INVENTION

The present invention relates to a method for the treatment of brain edema, comprising administering an effective amount of a composition comprising melatonin to a subject having brain edema. See the specification at page 7, fourth paragraph.

In one embodiment, the composition is a pharmaceutical composition and further comprises a pharmaceutically acceptable carrier. See the specification at page 14, fourth paragraph.

In another embodiment, melatonin is encapsulated in an encapsulating matrix or a liposome. See the specification at page 11, full paragraphs 1-4.

In another embodiment, the composition is orally administered. See the specification at page 13, second full paragraph.

In another embodiment, the composition is a food composition containing the melatonin and a food. See the specification at page 17, last paragraph.

In another embodiment, the food composition is selected from the group consisting of food, a food stuff and a composition comprising melatonin and an additive for incorporating melatonin in food. See the specification at page 17, last paragraph to page 18, third paragraph.

In another embodiment, the food composition is a cooked food, juice, ice cream, emulsified food, gelled food, or a fermented food. See the specification at page 17, last paragraph.

In another embodiment, the food composition is a fruit juice. See the specification at page 17, last paragraph.

VII. THE ISSUES OF THIS APPEAL

(1) Whether Claims 1-3, 7-8, and 12 are unpatentable under 35 U.S.C. §102(b) over WO 97/20555 (hereinafter referred to as "WO '555"). U.S. patent Nos. 5,137,871 (hereinafter referred to as "U.S. '871") and 5,520,912 (hereinafter referred to as "U.S. '912") were also cited as supporting references.

(2) Whether Claims 1-3, 7-8, and 12 are unpatentable under 35 U.S.C. §103(a) over WO '555.

(3) Whether Claims 8, 12, 16, and 17 are unpatentable under 35 U.S.C. §103(a) over WO '555 further in view of Wurtman, U.S. patent No. 4,687,763 (hereinafter referred to as "U.S. '763").

VIII. GROUPING OF THE CLAIMS

The claims do not stand and fall together. The reason for them not standing or falling together will be pointed out and discussed below.

IX. ARGUMENTS IN TRAVERSAL OF THE REJECTION

1. Claims 1-3, 7, 8, and 12 are Not Anticipated by WO '555

WO '555 fails to describe a method for the treatment of brain edema, comprising administering an effective amount of a composition comprising melatonin to a subject having brain edema as recited in Claim 1. In support of that position, Appellants submited an executed Declaration from Dr. Kunio Torii on August 28, 2003.

Dr. Torii is an inventor in the above-identified application. See paragraph (2) of the Declaration.

According to Dr. Torii, the field of the present invention is the pharmaceutical treatment of brain disorders. See paragraph (7) of the Declaration. Dr. Torii is an expert in that field. See paragraph (8) of the Declaration. He has worked in the field of the invention for more than 30 years and published many scientific articles as described in the *Curriculum Vitae* attached to the Declaration. See paragraph (8) of the Declaration.

According to Dr. Torii, there is no description in WO '555 of treating brain edema with melatonin. See paragraph (9) of the Declaration.

According to Dr. Torii, WO '555 describes a method for treating or preventing anoxic or ischemic brain injury by administering melatonin. See the Abstract of the reference and paragraph (10) of the Declaration. Dr. Torii points out that WO '555 does not mention brain edema at all. See paragraph (11) of the Declaration.

According to Dr. Torii, brain edema is a condition in which excess fluid accumulates in brain tissue, which results in the swelling of the brain tissue. See paragraph (12) of the Declaration. Dr. Torii points out that this is so is demonstrated by the specification of the above-identified application at page 1, lines 14-16 and U.S. '871 at column 3, lines 39-43. See paragraph (12) of the Declaration.

According to Dr. Torii, nowhere is it stated in WO '555 that the subjects described therein were suffering from the symptoms of brain edema described above. See paragraph (13) of the Declaration.

Dr. Torii notes that it is true that ischemia is a cause of brain edema. See paragraph (14) of the Declaration. However, Dr. Torii also points out that the fact that a subject has an ischemic brain injury does not mean that the subject must also have brain edema. See paragraph (14) of the Declaration. Thus, according to Dr. Torii, it is possible that a subject has an ischemic brain injury but does not have brain edema. See paragraph (14) of the Declaration.

In fact, according to Dr. Torii, there is no direct relationship between the clinical symptoms of ischemic patients and brain edema. See paragraph (15) of the Declaration. In Dr. Torii's opinion, this makes the clinical effect of melatonin on the brain uncertain. See paragraph (15) of the Declaration.

The Examiner appears to agree with Applicants' position. See paragraph (16) of the Declaration. At page 3, lines 6-9 of the Official Action dated December 2, 2002, the Examiner stated:

> Applicants argues that the subject has an ischemic brain injury does not mean that the subject has brain edema. ***This might be true***; however, if a person has ischemia caused by brain edema, then by treating the ischemia, one is treating the edema also and instant claims do not exclude the condition. [Emphasis added.]

However, Dr. Torii points out that there is nothing in WO '555 which suggests that the subjects treated with melatonin as described therein were suffering from brain edema. See paragraph (17) of the Declaration. Therefore, according to Dr. Torii, the Examiner is only speculating that the subjects described in WO '555 were also suffering from brain edema, in addition to ischemia. See paragraph (17) of the Declaration. Dr. Torii points out that there is no evidence in WO '555 which supports the Examiner's speculation, since there is no mention at all of brain edema in that publication. See paragraph (17) of the Declaration. Thus, the Examiner has failed to establish that the subjects described in WO '555 were necessarily suffering from brain edema. See paragraph (17) of the Declaration.

In addition, as shown at page 21 of WO '555, the mild 4-vessel occlusion model (which is also referred to as 4VO, 10 minute occlusion) was used to demonstrate the therapeutic efficacy in treating brain ischemia with melatonin. See paragraph (19) of the Declaration.

The 4VO model is not used by workers in the field of the invention to measure the therapeutic effect of an agent for treating brain edema. See paragraph (18) of the Declaration. This is because the 4VO model is well known in the field of the invention to suffer from a variety of problems relating to the identification of agents which are useful for treating brain edema. See paragraph (19) of the Declaration.

According to Dr. Torii, U.S. '871 describes a treatment to reduce edema for brain and musculature injuries. See the Abstract and paragraph (21) of the Declaration.

U.S. '871 at column 3, lines 39-51 states:

> Brain edema refers to a condition in which there is increased water content in brain tissue. This condition occurs when there is a breakdown in the function of blood vessels that normally separate blood constituents from brain tissue. Brain blood vessels become more permeable when they are injured by a lack of oxygen, by toxic substances generated in injured tissues, or by unknown causes such as those associated with

> brain hemorrhage of the newborn. The medical conditions associated with brain edema are: brain ischemia, brain infarction, brain tumors, brain infarctions and abscesses, brain trauma and contusions, and secondary brain damage arising from neurosurgical operations.

Thus, according to Dr. Torii, a subject suffering from brain edema may also be suffering from brain ischemia. See paragraph (23) of the Declaration.

However, as noted above, the fact that that a subject is suffering from brain ischemia does not necessarily mean that the subject is also suffering from brain edema. See paragraph (24) of the Declaration. In Dr. Torii's opinion, a subject may suffer from brain ischemia but not suffer from brain edema. See paragraph (24) of the Declaration. Again, as noted above, there is no direct relationship between the clinical symptoms of ischemic patients and brain edema. See paragraph (25) of the Declaration.

According to Dr. Torii, U.S. '912 describes the prevention and treatment of ischemic events and reperfusion injury resulting therefrom using Lys-plasminogen. See the Abstract and paragraph (26) of the Declaration.

Dr. Torii points out that at column 3, line 6 to column 4, line 6, U.S. '912 states that brain ischemia can cause brain edema. See paragraph (27) of the Declaration.

However, as discussed above, a subject suffering from brain ischemia does not necessarily also suffer from brain edema, i.e., a subject may suffer from brain ischemia but not suffer from brain edema. See paragraph (28) of the Declaration.

In view of the foregoing, WO '555 fails to describe, either explicitly or inherently, treating brain edema by administering melatonin to a subject having brain edema. Therefore, WO '555 fails to anticipate the method claimed in Claim 1.

Claim 3, which depends from Claim 2, specifies that melatonin is encapsulated in an encapsulating matrix or a liposome. The Examiner has failed to provide any evidence that WO '555 describes melatonin encapsulated in an encapsulating matrix or a liposome and, in

fact, that reference does not. Accordingly, the Examiner has failed to demonstrate that Claim 3 is anticipated by WO '555.

2. **Claims 1-3, 7-8, and 12 are Not Obvious over WO '555**

As discussed above, WO '555 fails to describe treating brain edema by administering melatonin to a subject having brain edema. In fact, the reference fails to mention brain edema at all.

In Dr. Torii's opinion, WO '555 would not have suggested a method of treating brain edema by administering melatonin to a subject having brain edema to one of ordinary skill in the field of the field of the invention at the time the above-identified application was filed in the U.S. See paragraph (20) of the Declaration. Dr. Torii's opinion is based on the facts that (a) a subject having an ischemic brain injury does not necessarily also have brain edema, (b) there is no direct relationship between the clinical symptoms of ischemic patients and brain edema which makes the clinical effect of melatonin on the brain uncertain. See paragraph (20) of the Declaration. Therefore, according to Dr. Torii, one of ordinary skill in the field of the field of the invention at the time the above-identified application was filed in the U.S could not have predicted with a reasonable expectation of success that melatonin could be used to treat brain edema based on the disclosure of WO '555. See paragraph (20) of the Declaration.

Based on the foregoing, the method recited in Claim 1 is not suggested by WO '555. Therefore, Claim 1 is not obvious over that reference.

Claim 3 depends from Claim 2 and specifies that melatonin is encapsulated in an encapsulating matrix or a liposome. The Examiner has failed to provide any evidence that WO '555 describes melatonin encapsulated in an encapsulating matrix or a liposome and, in fact, that reference does not. Moreover, the Examiner has not provided any argument that

WO '555 suggests melatonin encapsulated in an encapsulating matrix or a liposome. Accordingly, the Examiner has failed to demonstrate that Claim 3 is anticipated by WO '555.

3. **Claims 8, 12, 16, and 17 are Not Obvious over WO '555 in view of U.S. '763**

As discussed under (1) and (2) above, WO '555 fails to describe or suggest the claimed method.

According to Dr. Torii, U.S. '763 describes a composition and method for increasing levels or release of brain serotonin. See the Abstract of the patent and paragraph (29) of the Declaration. The composition contains melatonin. See the Abstract and paragraph (29) of the Declaration.

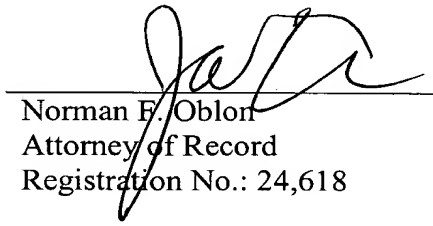
In Dr. Torii's opinion, U.S. '763 fails to describe or suggest administering melatonin to treat brain edema, since that patent fails to mention brain edema at all. See paragraph (30) of the Declaration. Therefore, U.S. '763 fails to remedy the deficiencies of WO '555 described above. In view of these facts, it is Dr. Torii's opinion that WO '555 taken in any combination with U.S. '763 fails to suggest a method of treating brain edema by administering melatonin to a subject having brain edema to one of ordinary skill in the field of the field of the invention at the time the above-identified application was filed in the U.S. See paragraph (31) of the Declaration. Based on the foregoing, the method recited in Claims 8, 12, 16, and 17 is not suggested by WO '555 in view of U.S. '763. Therefore, those claims are not obvious over that combination references.

X. RELIEF REQUESTED

Reversal of the Examiner's rejections of the appealed claims under 35 U.S.C. § 102(b) and 35 U.S.C. § 103(a) is requested.

Respectfully Submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER, & NEUSTADT, P.C.



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APPENDIX I

The appealed claims read as follows:

1. A method for the treatment of brain edema, comprising administering an effective amount of a composition comprising melatonin to a subject having brain edema.

2. A method as claimed in claim 1, wherein the composition is a pharmaceutical composition and further comprises a pharmaceutically acceptable carrier.

3. A method as claimed in claim 2, wherein melatonin is encapsulated in an encapsulating matrix or a liposome.

7. A method as claimed in claim 1, wherein the composition is orally administered.

8. A method as claimed in claim 1, wherein the composition is a food composition containing the melatonin and a food.

12. A method as claimed in claim 8, wherein the food composition is selected from the group consisting of food, a food stuff and a composition comprising melatonin and an additive for incorporating melatonin in food.

16. The method of Claim 8, wherein the food composition is a cooked food, juice, ice cream, emulsified food, gelled food, or a fermented food.

17. The method of Claim 8, wherein the food composition is a fruit juice.